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IN THE EUROPEAN PATENT OFFICE

In re PCT International Application No.:	**PCT/CA2004/000493**
Filed:	**02 April 2004**
Applicant:	**CANADIAN BLOOD SERVICES**
Title:	**USE OF COAGULATION PROTEINS TO LYSE CLOTS**
Classification:	
Examiner:	
Applicant's Agent:	**Jennifer Holly** **Ogilvy Renault** **(613) 780-8678**

International Searching Authority
EUROPEAN PATENT OFFICE
DG-2
Erhardstrasse 27
D-80298 Munich
GERMANY

International Preliminary Examining Authority

AMENDMENT/RESPONSE UNDER ARTICLE 34 PCT

Dear Sirs:

In response to a Written Opinion dated August 12, 2004 please amend the above-identified patent application as follows:

IN THE CLAIMS:

Please amend the pages of claims presently on file and replace with new pages enclosed herewith.

REMARKS

The Examiner has objected to claims 1 -17, and 20-23 as being anticipated as well as lacking inventiveness in view of the disclosures of D1 - D10. Applicant respectfully traverses

the Examiner's objections in this regard. In addition, claim 20 is herein amended to more definitively claim the subject matter thereof.

In response to the Examiner's objections in view of the cited references, Applicant submits that the present invention is directed to a method for accelerating blood clot dissolution by administering to a patient in need thereof, a coagulation protein comprising a basic C-terminal amino acid. Applicant believes that the role of a coagulation protein in stage 2 of fibrin clot lysis has not been previously disclosed prior to the present invention. According to preferred embodiment of the present invention, the coagulation protein is a derivative of Factor X or Factor V or a combination thereof.

Specifically, the state-of-the-art in tissue plasminogen activator (tPA)-dependent clot lysis can be simplified into a two stage process.

Stage 1: tPA requires the availability of a coFactor to accelerate the proteolytic conversion of inactive plasminogen to the active form, plasmin.

Stage 2: Plasmin cleaves the insoluble fibrin clot into soluble fragments for physiological clearance.

While several coFactors have been identified in the prior art that will satisfy Stage 1 of clot lysis as outlined above, only fibrin itself is generally believed to have physiological relevance as a tPA coFactor to facilitate the essential Stage 2 of clot lysis. The reason for this dogmatic view is the logical presumption that huge concentrations of fibrin at the site of a clot would vastly overwhelm any contribution of other tPA coFactors, making the latter irrelevant *in vivo*. Surprisingly, Applicants have found that their previously reported participation of Factor Xa or Factor Va in Stage 1 of clot lysis (as reported in documents D6 – D10), also plays a significant physiological role in the cleavage of a fibrin clot (figure 2), namely Stage 2 of clot lysis.

Applicants respectfully submit that a prior disclosure that derivatives of Factor X or Factor V can accelerate tPA-dependent plasmin generation in Stage 1, does not negate the

novelty nor make obvious the basis of the present invention, whereby a coagulation protein comprising a basic C-terminal amino acid is shown to play a physiological role in Stage 2 clot lysis. It is on this basis that Applicant submits the present invention distinguishes over the teaching of the prior art, and D1 – D10, in particular. Thus, Applicant submits that the claims as herein provided are both novel and unobvious in view thereof.

Specifically, D1 describes anticoagulant Factor Va derivatives. That is, D1 claims the use of either Factor Va cleaved at Arg506 by activated protein C or analogous recombinant forms to inhibit clot formation (i.e. anticoagulation). Alternatively, the present application discloses a role of a coagulation protein comprising a basic C-terminal amino acid directly in clot lysis, not anticoagulation. Furthermore, the derivatives of Factor Va of the present invention are based on different cleavages which are induced by a different enzyme, plasmin.

D2 discloses a stable preparation for the treatment of blood coagulation disorders, comprising an activated coagulation Factor and lipid vesicles. Specifically, this reference uses compositions of phospholipid vesicles to stabilize clotting Factors, including Factor Xa, for subsequent virus-inactivation procedures. D3 discloses a virus-inactivated Factor Xa preparation. This reference describes the use of a phospholipid to stabilize clotting Factor X during heat inactivation of viruses for subsequent activation to Factor Xa. The resulting composition was envisaged as a virus-free clot-inducing agent to treat hemophiliacs. The teaching of D2 and D3 do not relate to the compositions disclosed in accordance with the present application which are shown to enhance clot lysis, the opposite of clot-induction.

D4 describes the preparation and use of Factor Xa inactivated at the chemical catalysis site for use as an anticoagulant treatment. This has no relation to the use of a coagulation protein comprising a basic C-terminal amino acid in clot lysis in accordance with the present invention.

D5 describes a clot-inducing composition of Factor Xa and phospholipids to stimulate clot formation, which then triggers a fibrinolytic response by increasing the secretion of tPA from cells. According to this reference, derivatives of Factor Xa do not act to directly enhance tPA activity. In essence, Applicants contest that the approach of D5 effectively teaches away from the present invention on the basis that the disclosed Factor Xa compositions serve to effect clot-induction to achieve the desired result. Alternatively, the present invention teaches of a coagulation protein comprising a basic C-terminal amino, as exemplified by a Factor Xa derivative, functioning as a tPA-specific coFactor. The proteins of the present invention are, not only shown to accelerate plasmin formation, but to also play a physiological role in the lysis of a fibrin clot.

Applicant notes that documents D6-D10, as cited in the International Search Report are earlier publications of the inventors themselves. Although these prior publications relate in-part to the subject matter of the present patent application, Applicant submits that the underlying feature of the claimed subject matter of the present application was not previously disclosed in these references. Documents D6 – D10 do not demonstrate that a coagulation protein comprising a basic C-terminal amino acid can facilitate a direct effect on the lysis of a fibrin clot (i.e. Stage 2, above), as shown in accordance with the present invention (Figure 2). Documents D6 – D10 are restricted to the role of the derivatives of these clotting Factors in Stage 1 of clot lysis whereby they can act to enhance plasmin production by tPA.

Applicant also reports that the unobviousness of the present invention has been demonstrated by unsuspecting and doubtful comments received from persons skilled in the art relating to the potential success of the present invention. These persons skilled in the art doubted that Stage 2 (above) would be facilitated by derivatives of clotting Factors despite the role there of in Stage 1. This skepticism was muted with the findings as presented in the present application, and as exemplified by the data of Figure 2.

The subject matter of original claims 20 is herein amended to more definitely claim a pharmaceutical composition for accelerating blood clot dissolution, according to a preferred embodiment of the present invention.

In accordance with the above comments and amendments, Applicant believes the claims of the present application both distinguish over and warrant patentability in view of the prior art.

Claims 18 and 19 are directed to a "method for detecting a fibrinolytic potential in a subject" comprising "measuring a relative concentration of a coagulation protein". The ISA has deemed these expressions unclear and lacking support in the description, while advising that a search pertaining to the subject matter of these claims was not able to be conducted. Applicant believes that the objected terminology is both supported by the teachings of the present application and would be clearly understood to a person of skill in the art, in view of the disclosure of the present application. Specifically, a definition of the fibrinolysis pathway appears on page 1, line 11-13, while a discussion of "fibrinolytic potential" and its correlation to "fibrinolytic activity" appears on page 12, lines 1 – 12 of the present application. Thus, Applicant believes the objected terminology to be clear and fully supported thereby. Furthermore, in view of the teachings of the present invention (Figure 3, for example), Applicant believes that the terminology "fibrinolytic potential" would be understood by a person of skill in the art to refer to a measure of an individual's ability to lyse clots by correlation to the amount of a coagulation protein (such as, Factor Xa-derived tPA coFactors, for example) detected in a subject's plasma.

Likewise, with respect to the term "relative" as appearing in claims 18 and 19, Applicant points to the teaching of the present application at page 2, lines 21 -30 wherein the context of this term would be clear to a person of skill in the art.

Furthermore, the ISA has indicated that the claimed expression "coagulation protein comprising a basic C-terminal amino acid" fails to adequately define the envisaged substance

of the present application. As a result, the ISA has limited their search to the subject matter of Factor Xa, alpha, beta and gamma and Factor Va. Applicant respectfully traverses the basis of this restriction. Applicant believes that the present application adequately exemplifies a representative number of the claimed coagulation proteins comprising a basic C-terminal amino acid, such as derivatives of Factor Xa, alpha, beta and gamma and Factor Va, so as to support the breadth of claims herein provided.

It is respectfully submitted that no new subject matter has been introduced in the claims as a result of the amendments and support for the amendments have been indicated above.

In light of the foregoing, it is believed that the claims as herein amended fully satisfy the requirements for Novelty, Inventive Step, and Industrial Applicability. If, for any reason, the Examiner does not concur, then the Examiner is respectfully requested to issue a second Written Opinion in this matter.

Respectfully,
Canadian Blood Services

OGILVY RENAULT
Signed by Jennifer Quinn
Patent Agent of the firm

JH:bd